noteworthy that most of these effects involve a latent period of about a decade. In most instances no detectable objective basis for anticipating the ultimate carcinogenic response is apparent during the period of latency.

It is also noteworthy that all known carcinogenic agents for man have been shown to be also carcinogenic in animals. Hence common pathogenetic factors are clearly involved in the development of cancer in man and in animals. Consequently, we cannot ignore the regularly observed length of latency and the known parallelisms in the genesis of cancer in man and animals in evaluating what is known to date about the carcinogenic potential of the steroid substances under discussion.

Estrogens and Breast Cancer

Ovariectomy induces remissions in 30 to 50 percent of young women with breast cancer (*7*). It is generally agreed that this ablative procedure exerts its favorable effects through a reduction of estrogen formation in the body (*8*). Moreover, urinary excretion studies show that the amounts of estrogen involved must be measured in microgram quantities (*8*). Less direct evidence indicates that in some women estrogen administration in doses comparable to those contained in the currently marketed oral contraceptives will transiently stimulate the metabolic activity of metastatic breast cancer, but such stimulation is not always related to an impairment in the clinical course (*9, 10, 11*). Accordingly, it is universal clinical practice to prohibit the use of such materials by young women with a known breast cancer. Paradoxically, this restriction is not applicable to older women with breast cancer since a substantial proportion of such older women, and less commonly certain younger women, experience regression of a preexisting breast cancer when given estrogens (*11, 18, 29*). It is therefore clear that both endogenous and exogenous estrogen will modify the activity of established cancer in women.

The proponents of the use of these agents state that these considerations pertain only to "preexisting" breast cancer. Such an inference is untenable in view of the fact that other malignancies in women, such as cancer of the cervix and endometrium, have a prolonged pathogenetic phase involving many years. Unfortunately, we have no direct knowledge of the preclinical or pathogenetic phase of breast cancer in young women, nor do we know the effects of exogenous estrogens upon this process. Indirect evidence from mammography studies indicates however, that the pathogenetic phase can occupy several years (*12a*). Hence it seems reasonable to consider whether or not the repeated induction of a hyperestrogenic state implies any risk of exacerbation of this occult phase of breast cancer since such agents can significantly alter the established disease process in some women.

It is frequently stated that although estrogens have been employed clinically for 25 years, the incidence of breast cancer in women has not materially changed and that only an extremely limited number of cases of breast cancer in women have been reported to be specifically associated with estrogen therapy (*13–17*). These generalizations ignore some serious limitations in our epidemiological knowledge over the past 25 years.

Firstly, past clinical experience relates almost entirely to the use of estrogens for the control of symptoms in women of menopausal or postmenopausal age. In addition, a very limited number of younger women suffering from artificially induced menopause, ovarian insufficiency, menstrual disorders, and other gynecological problems have also been treated. We know, however, from differences in response of established breast cancer to estrogen therapy in older women as contrasted with that seen in menstruating women, that it is not valid to equate a past experience in predominantly older patients with what should be anticipated in younger women, especially with respect to breast cancer. This difference in response is clearly reflected in the remarkable increase in estrogen-induced regressions in breast cancer with increasing age (*18*).

The study of Kennedy on the dual effects of estrogen on breast cancer in women aged 35 to 54 also emphasizes the critical role of both age and dosage in determining whether the response of breast cancer to estrogen administration will be exacerbation or regression (*11*). Thus, Kennedy states: "In premenopausal women with breast cancer or in patients in whom castration produced a regression of tumor, there is no doubt that small physiological doses of estrogenic hormone may stimulate the growth of cancer," and further: "It might, therefore, be postulated that the estrogenic hormone has a dual action: stimulation of cancer cell growth by small doses, and a more potent inhibitory effect on cell growth in large doses" (*11*).

Secondly, because of the absence of specific data